More specifically, claims 1-6, 9-11, 14 and 17 are being amended to convert the Swiss-type use claim to the U.S. method of treatment format. Claim 16 is being amended to convert the European style pharmaceutical composition claim into the U.S. format. Applicants submit that all of these amendments do not change the scope of the claims as originally filed, because the amendments are being made solely to place the claims in a format appropriate for U.S. prosecution. Such amendments are therefore made to address formalities in the claim format and are not related to the patentability of the subject matter of the claims.

Conclusion

Applicants believe that the subject matter of the pending claims is patentable and that the instant application should accordingly be allowed. If the Examiner believes that a conversation with Applicants' attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned attorney at (203) 812-3964.

Respectfully submitted,

Dated: June 29, 2001

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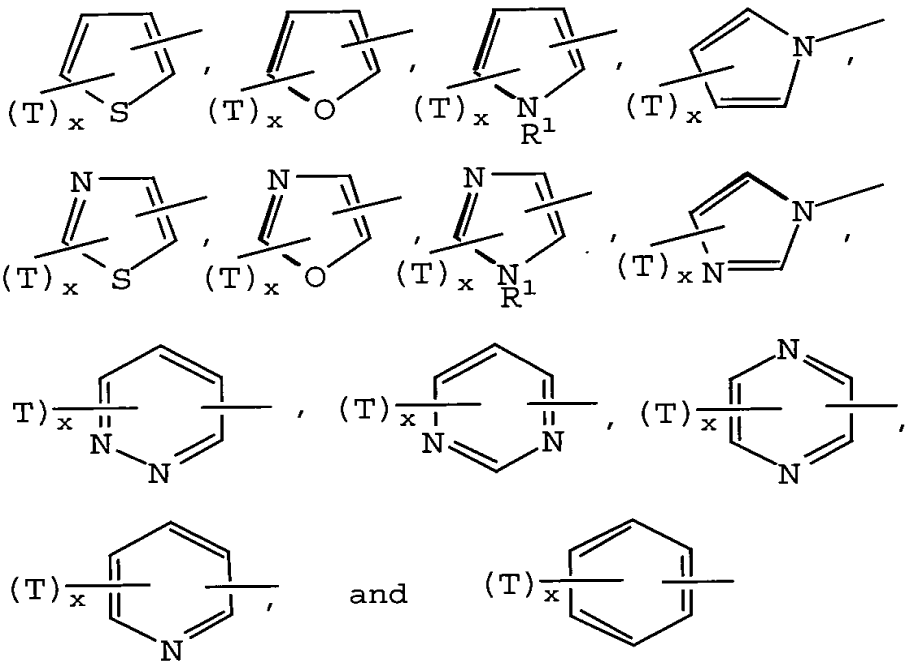
1. (Amended) A method of treating or preventing a respiratory disease, comprising administering to a mammal an effective amount of a compound [Use of compounds] having matrix metalloprotease inhibitory activity and the generalized formula:

$$(T)_XA\text{-}B\text{-}D\text{-}E\text{-}CO_2H$$

wherein

(a) $(T)_XA$ represents a substituted or unsubstituted aromatic or hetero-aromatic moiety selected from the group consisting of:



wherein R^1 represents H or alkyl of 1 - 3 carbons; and

each T represents a substituent group, independently selected from the group consisting of:

* the halogens -F, -Cl, -Br, and -I;

* alkyl of 1 - 10 carbons;
* haloalkyl of 1 - 10 carbons;
* haloalkoxy of 1 - 10 carbons;
* alkenyl of 2 - 10 carbons;
* alkynyl of 2 - 10 carbons;
* $-(CH_2)_pQ$, wherein
  p is 0 or an integer 1 - 4,
* -alkenyl-Q, wherein
  said alkenyl moiety comprises 2 - 4 carbons, and
* -alkynyl-Q , wherein
  said alkynyl moiety comprises 2 - 7 carbons; and

Q is selected from the group consisting of aryl of 6 - 10 carbons, heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, -CN, -CHO, $-NO_2$, $-CO_2R^2$, $-OCOR^2$, $-SOR^3$, $-SO_2R^3$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-C(O)R^2$, $-N(R^4)_2$, $-N(R^2)COR^2$, $-N(R^2)CO_2R^3$, $-N(R^2)CON(R^4)_2$, $-CHN_4$, $-OR^4$, and $-SR^4$;

wherein

R^2 represents H;
alkyl of 1 - 6 carbons;
aryl of 6 - 10 carbons;
heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom; or
arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons; or
heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

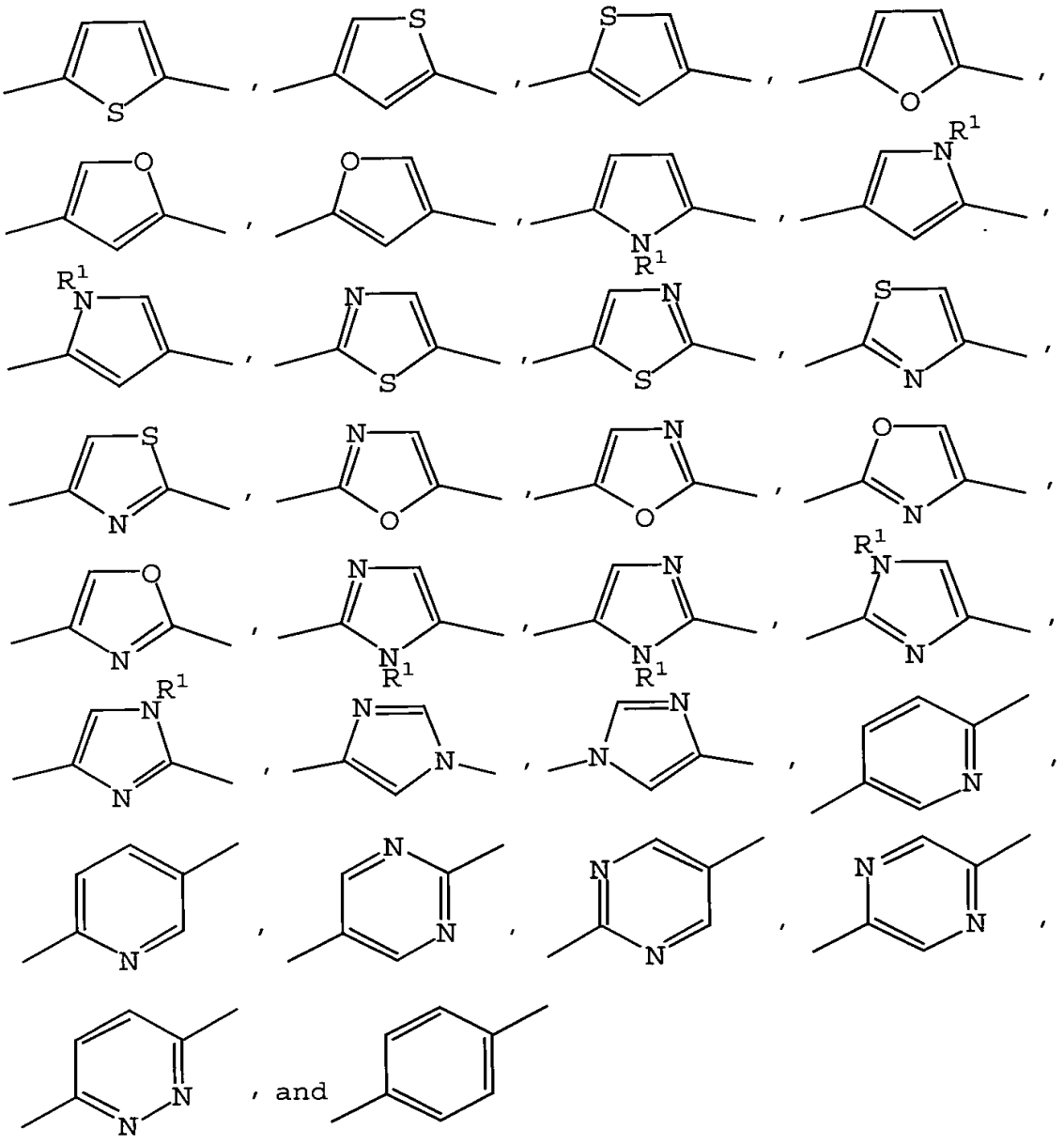
R^3 represents alkyl of 1 - 4 carbons;
aryl of 6 - 10 carbons;
heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom; or
arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons; or
heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

R^4 represents H;
alkyl of 1 - 12 carbons;
aryl of 6 - 10 carbons;
heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;
arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons;
heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;
alkenyl of 2 - 12 carbons;
alkynyl of 2 - 12 carbons;
$-(C_qH_{2q}O)_rR^5$ wherein q is 1-3; r is 1 - 3; and R^5 is H provided q is greater than 1, or alkyl of 1 - 4 carbons, or phenyl;
alkylenethio terminated with H, alkyl of 1-4 Carbons, or phenyl;
alkyleneamino terminated with H, alkyl of 1-4 carbons, or phenyl;
$-(CH_2)_SX$ wherein s is 1 - 3 and X is halogen;
$-C(O)OR^2$; or
$-C(O)R^2$;

and with the provisos that a) when two R^4 groups are situated on a nitrogen, they may be joined by a bond to form a heterocycle, and b) unsaturation in a moiety which is attached to Q or which is part of Q is separated from any N, O, or S of Q by at least one carbon atom, and

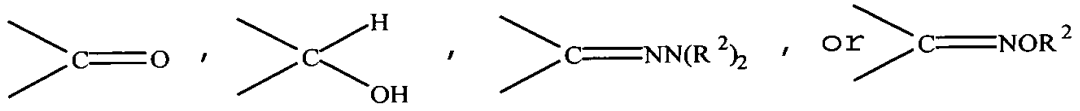
x is 0, 1, or 2;

(b) B represents a bond or an optionally substituted aromatic or hetero-aromatic ring containing 0-2 substituents T, which substituents T may independently have the meaning specified under (a), the B rings being selected from the group consisting of:



wherein R^1 is as defined above;

(c) D represents



in which R^2 is defined as above and each R^2 may be the same or different ;

(d) E represents a chain of n carbon atoms bearing m substituents R^6, wherein said R^6 groups are independent substituents, or constitute spiro or nonspiro rings in which a) two groups R^6 are joined, and taken together with the chain atom(s) to which said two R^6 group(s) are attached, and any intervening chain atoms, constitute a 3 - 7 membered ring, or b) one group R^6 is joined to the chain on which said one group R^6 resides, and taken together with the chain atom(s) to which said R^6 group is attached, and any intervening chain atoms, constitutes a 3 - 7 membered ring; and wherein

n is 2 or 3;

m is an integer of 1 - 3;

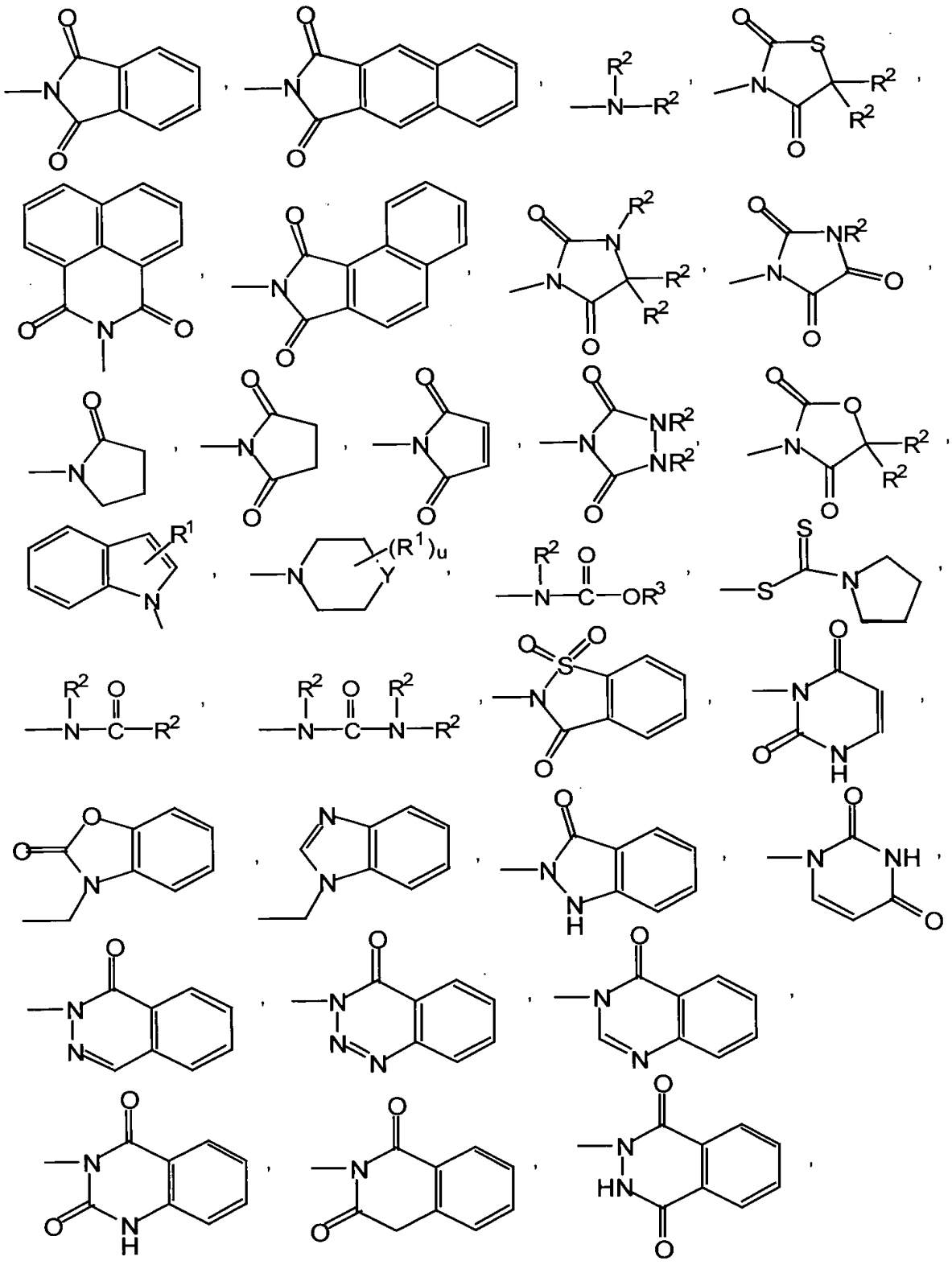
each group R^6 is independently selected from the group consisting of:

* fluorine;
* hydroxyl, with the proviso that a single carbon may bear no more than one hydroxyl substituent
* alkyl of 1 - 10 carbons;
* aryl of 6 - 10 carbons;
* heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;
* arylalkyl wherein the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 8 carbons;
* heteroaryl-alkyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 - 8 carbons;
* alkenyl of 2 - 10 carbons;
* aryl-alkenyl wherein the aryl portion contains 6 - 10 carbons and the alkenyl portion contains 2 - 5 carbons;
* heteroaryl-alkenyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkenyl portion contains 2 -5 carbons;
* alkynyl of 2 - 10 carbons;

* aryl-alkynyl wherein the aryl portion contains 6 - 10 carbons and the alkynyl portion contains 2 - 5 carbons;
* heteroaryl-alkynyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkynyl portion contains 2 - 5 carbons;
* $-(CH_2)_tR^7$ wherein

  t is 0 or an integer of 1 - 5; and

  R^7 is selected from the group consisting of



and corresponding heteroaryl moieties in which the aryl portion of an aryl-containing R^7 group comprises 4 - 9 carbons and at least one N, O, or S heteroatom;

wherein

Y represents O or S;

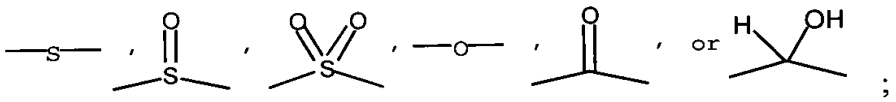
R^1, R^2, and R^3 are as defined above; and

u is 0, 1, or 2; and

* $-(CH_2)_vZR^8$ wherein

v is 0 or an integer of 1 to 4; and

Z represents



;

R^8 is selected from the group consisting of:

alkyl of 1 to 12 carbons;

aryl of 6 to 10 carbons;

heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;

arylalkyl wherein the aryl portion contains 6 to 12 carbons and the alkyl portion contains 1 to 4 carbons;

heteroaryl-alkyl wherein the aryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

$-C(O)R^9$ wherein R^9 represents alkyl of 2 - 6 carbons, aryl of 6 - 10 carbons, heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, or arylalkyl in which the aryl portion contains 6 - 10 carbons or is heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 - 4 carbons;

and with the provisos that

- when R^8 is $-C(O)R^9$, Z is S or O;
- when Z is O, R^8 may also be $-(C_qH_{2q}O)_rR^5$ wherein q, r, and R^5 are as defined above; and

* $-(CH_2)_wSiR^{10}{}_3$ wherein
  w is an integer of 1 to 3; and
  R^{10} represents alkyl of 1 to 2 carbons;

and with the proviso that

- aryl or heteroaryl portions of any of said T or R^6 groups optionally may bear up to two substituents selected from the group consisting of $-(CH_2)_yC(R^4)(R^3)OH$, $-(CH_2)_yOR^4$, $-(CH_2)_ySR^4$, $-(CH_2)_yS(O)R^4$, $-(CH_2)_yS(O)_2R^4$, $-(CH_2)_ySO_2N(R^4)_2$, $-(CH_2)_yN(R^4)_2$, $-(CH_2)_yN(R^4)COR^3$, $-OC(R^4)_2O-$ in which both oxygen atoms are connected to the aryl ring, $-(CH_2)_yCOR^4$, $-(CH_2)_yCON(R^4)_2$, $-(CH_2)_yCO_2R^4$, $-(CH_2)_yOCOR^4$, -halogen, -CHO, $-CF_3$, $-NO_2$, -CN, and $-R^3$, wherein
  y is 0 - 4; and
  R^3 and R^4 are defined as above; and any two R^4 which are attached to one nitrogen may be joined to form a heterocycle;

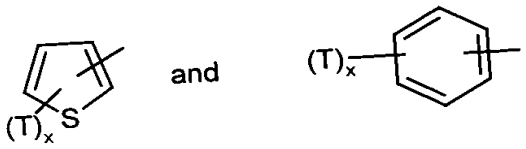
and pharmaceutically acceptable salts and prodrugs thereof [for the manufacturing of drugs for the treatment and prevention of respiratory diseases].

2. (Amended) <u>The method of</u> [Use of compounds according to] claim 1 [having matrix metalloprotease inhibitory activity and the generalized formula:

$$(T)_xA\text{-}B\text{-}D\text{-}E\text{-}CO_2H]$$

wherein

(a) $(T)_xA$ represents a substituted or unsubstituted aromatic or hetero-aromatic moiety selected from the group consisting of:



wherein

each T represents a substituent group, independently selected from the group consisting of:

* the halogens -F, -Cl, -Br, and -I;
* alkyl of 1 - 10 carbons;
* haloalkyl of 1 - 10 carbons;
* alkenyl of 2 - 10 carbons;
* alkynyl of 2 - 10 carbons;
* $-(CH_2)_pQ$, wherein
  p is 0 or an integer 1 - 4,
* -alkenyl-Q, wherein
  said alkenyl moiety comprises 2 - 4 carbons, and
* -alkynyl-Q , wherein
  said alkynyl moiety comprises 2 - 7 carbons; and

Q is selected from the group consisting of $-OR^4$ and $-SR^4$;

wherein

R^4 represents H;
alkyl of 1 - 12 carbons;
aryl of 6 - 10 carbons;
heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;
arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons;

heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

$-C(O)OR^2$; or

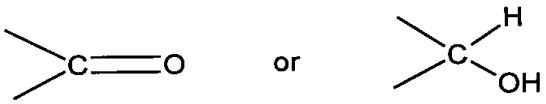
$-C(O)R^2$;

and with the proviso that unsaturation in a moiety which is attached to Q or which is part of Q is separated from any N, O, or S of Q by at least one carbon atom, and

x is 0, 1, or 2;

(b) B represents an optionally substituted phenyl or thienyl ring containing 0-2 substituents T, which substituents T may independently have the meaning specified under (a).

(c) D represents



(d) E represents a chain of n carbon atoms bearing m substituents R^6, wherein said R^6 groups are independent substituents, or constitute nonspiro rings in which two groups R^6 are joined, and taken together with the chain atom(s) to which said two R^6 group(s) are attached, and any intervening chain atoms, constitute a 5 or 6- membered ring; and wherein

n is 2 or 3;

m is an integer of 1 or 2;

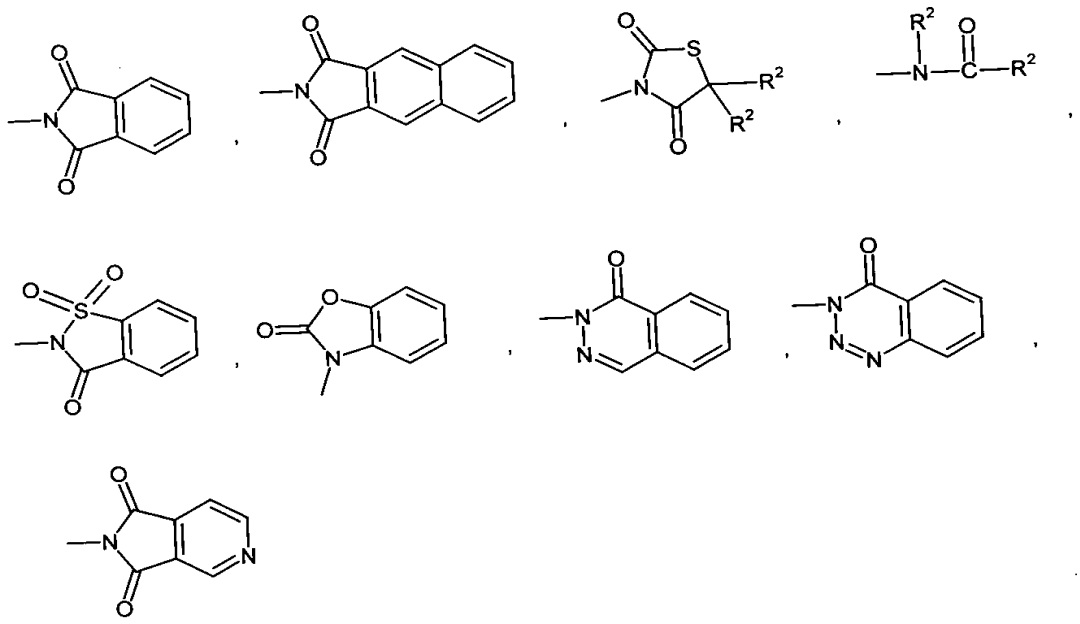
each group R^6 is independently selected from the group consisting of:

* arylalkyl wherein the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 8 carbons;

* -$(CH_2)_tR^7$ wherein

t is 0 or an integer of 1 - 5; and

R^7 is selected from the group consisting of



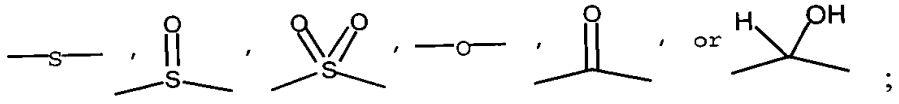
wherein

R^2 is independently selected from the group consisting of: H; aryl of 6-10 carbons

* -$(CH_2)_vZR^8$ wherein

v is 0 or an integer of 1 to 4; and

Z represents



;

R^8 is selected from the group consisting of:

alkyl of 1 to 12 carbons;

aryl of 6 to 10 carbons;

[redacted]aryl comprising 4 - 9 carbons and at l[redacted]one N, O, or S heteroatom;

arylalkyl wherein the aryl portion contains 6 to 12 carbons and the alkyl portion contains 1 to 4 carbons;

heteroaryl-alkyl wherein the aryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

$-C(O)R^9$ wherein R^9 represents alkyl of 2 - 6 carbons, aryl of 6 - 10 carbons, heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, or arylalkyl in which the aryl portion contains 6 - 10 carbons or is heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 - 4 carbons;

and with the provisos that

- when R^8 is $-C(O)R^9$, Z is S or O;
- when Z is O, R^8 may also be $-(C_qH_{2q}O)_rR^5$ wherein q, r, and R^5 are as defined above; and

* $-(CH_2)_wSiR^{10}{}_3$ wherein

  w is an integer of 1 to 3; and

  R^{10} represents alkyl of 1 to 2 carbons;

and with the proviso that

- aryl or heteroaryl portions of any of said T or R^6 groups optionally may bear up to two substituents selected from the group consisting of OR^4, $N(R^4)_2$, $-OC(R^4)_2O-$ in which both oxygen atoms are connected to the aryl ring, $CON(R^4)2$, $OCOR^4$, -halogen, $-NO_2$, and alkyl with up to 6 carbon atome wherein

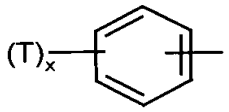
R^4 is defined as above;

and pharmaceutically acceptable salts and prodrugs thereof [for the manufacturing of drugs for the treatment and prevention of respiratory diseases].

3. (Amended) The method [Use of a compound] of claim 1 or 2, wherein at least one of the units A, B, T, and R^6 comprises a heteroaromatic ring [for the manufacturing of drugs for the treatment and prevention of respiratory diseases].

4. (Amended) The method [Use of a compound] of claim 1or 2, wherein in said E unit, n is 2 and m is 1 [for the manufacturing of drugs for the treatment and prevention of respiratory diseases].

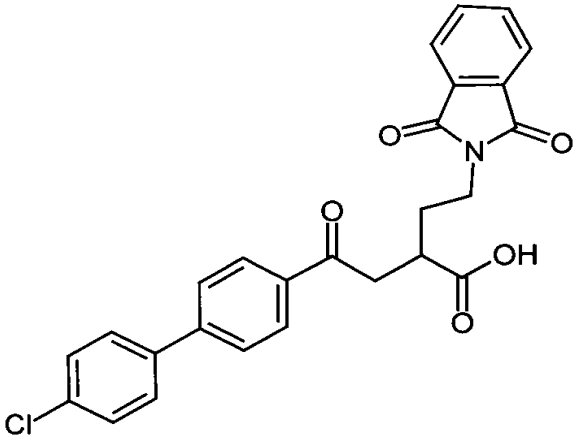
5. (Amended) The method [Use of a compound] of claim 1or 2, wherein A is

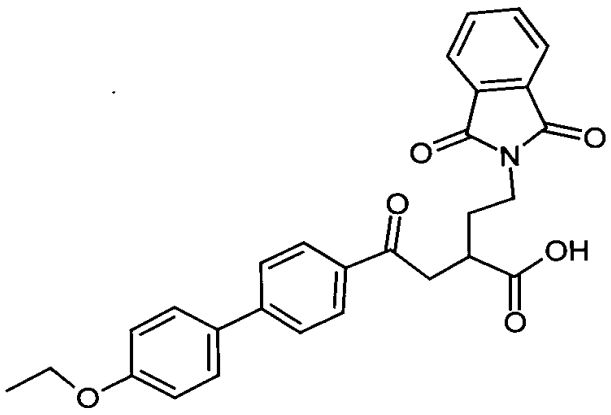


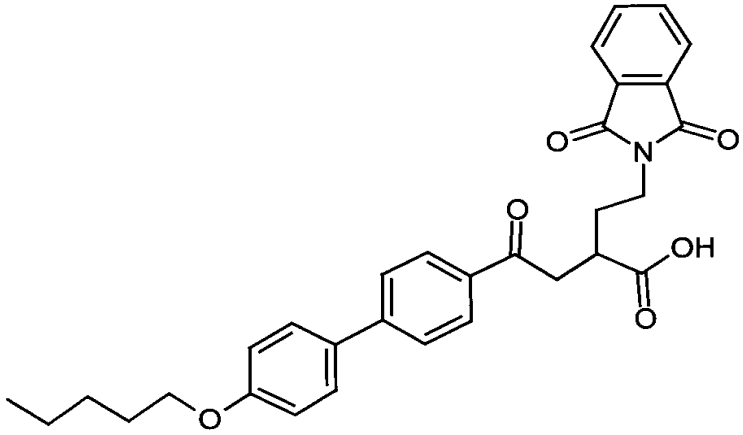
;

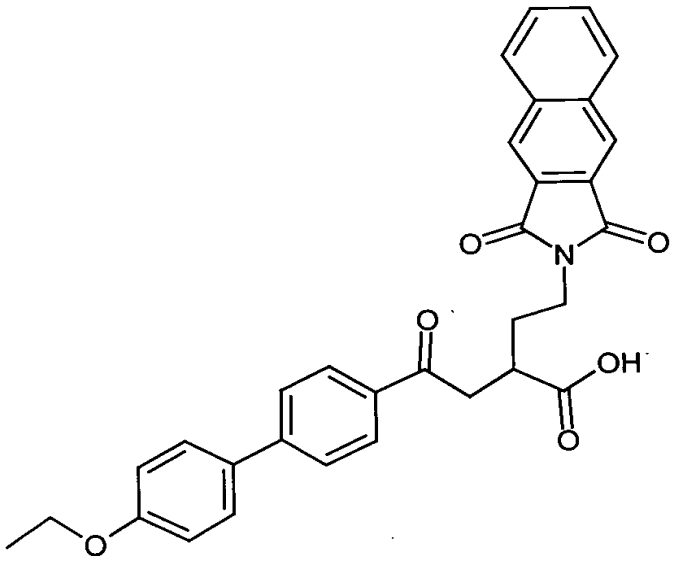
B is p-phenylene and D is a carbonyl group [for the manufacturing of drugs for the treatment and prevention of respiratory diseases].

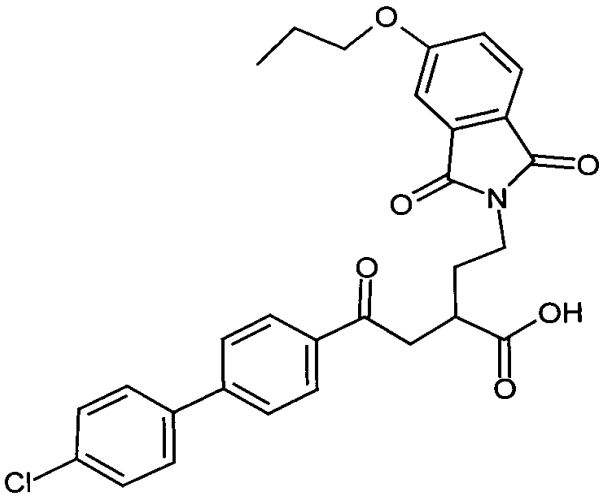
6. (Amended) The method [Use of a compound] of claim 1 or 2, wherein the compound is selected from the following group:

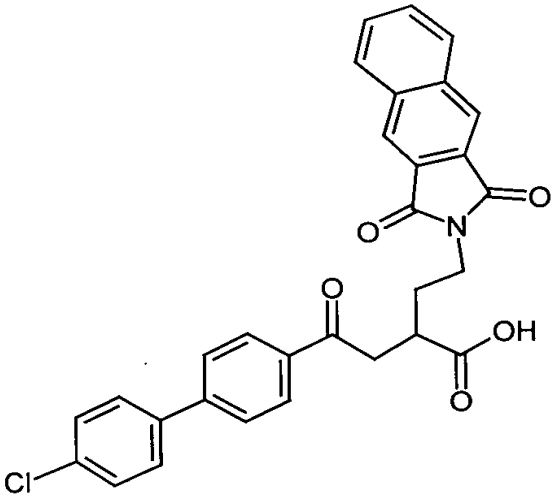


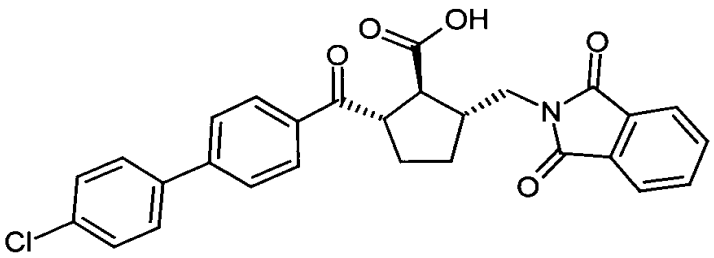


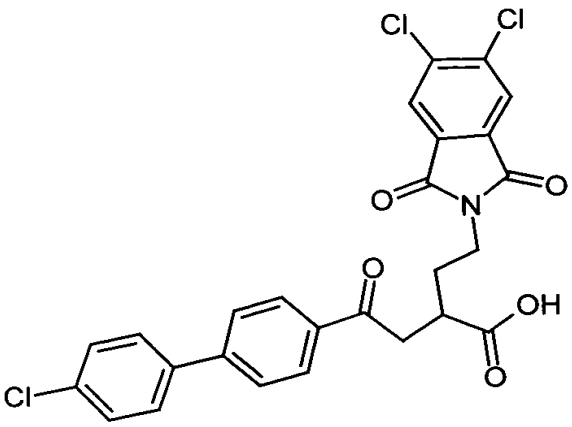


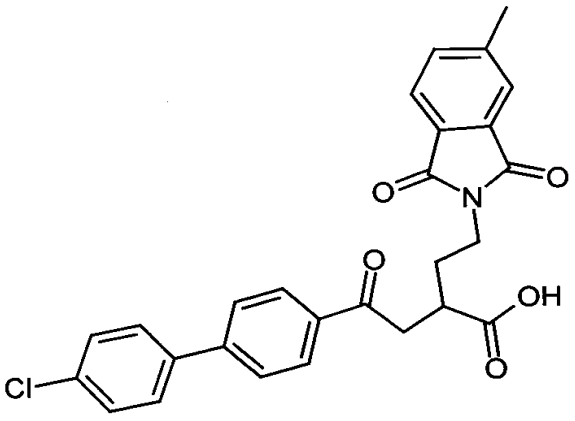


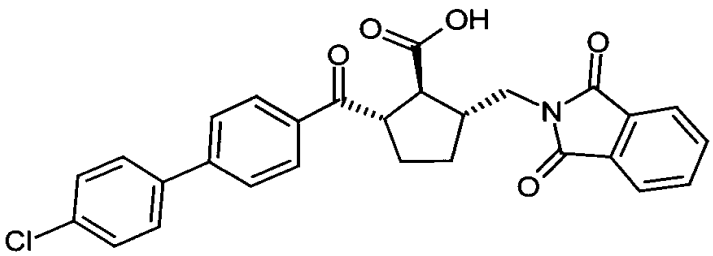


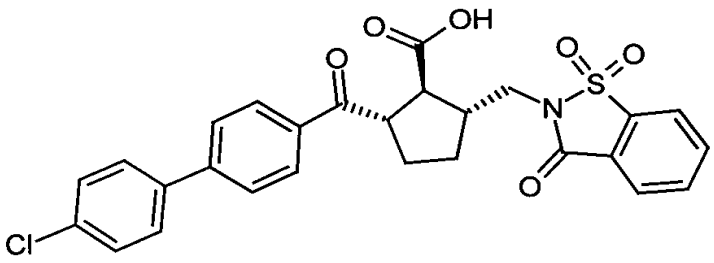


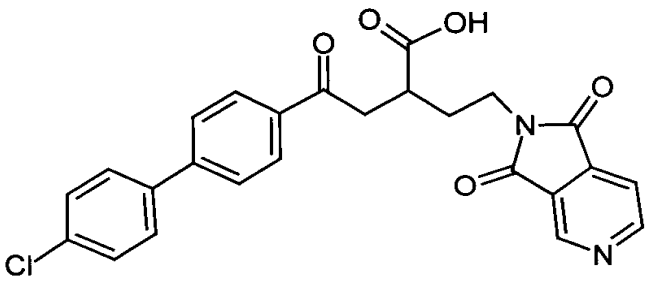


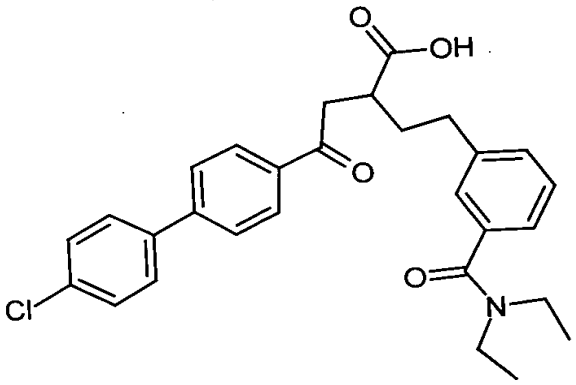


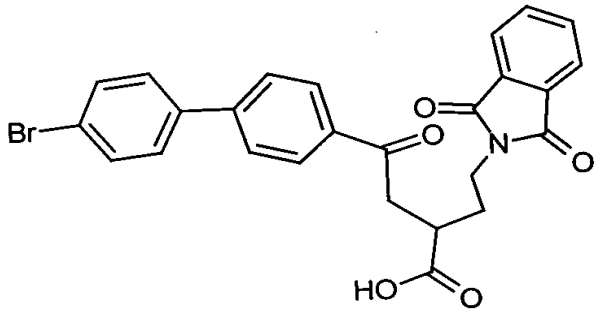


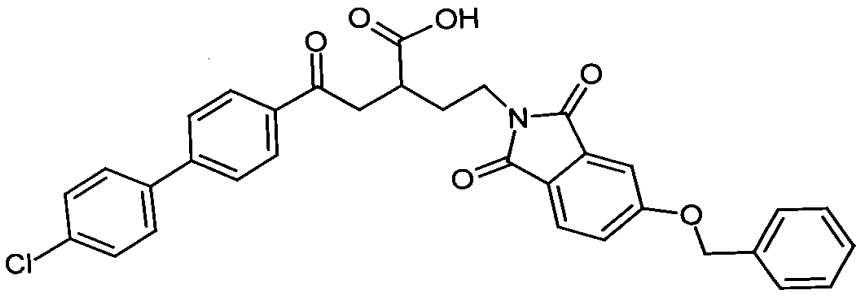


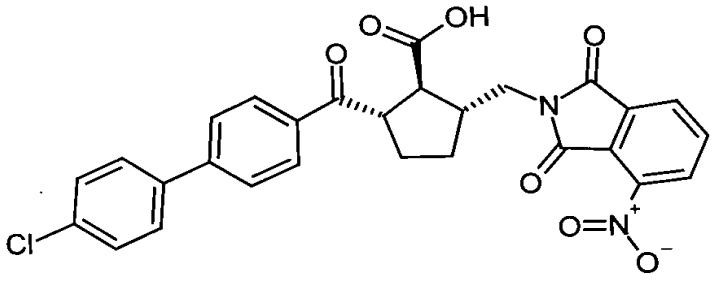


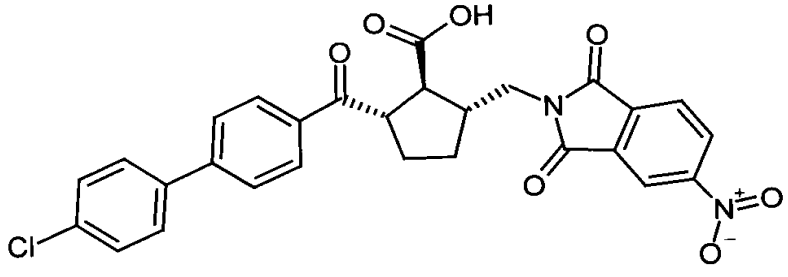


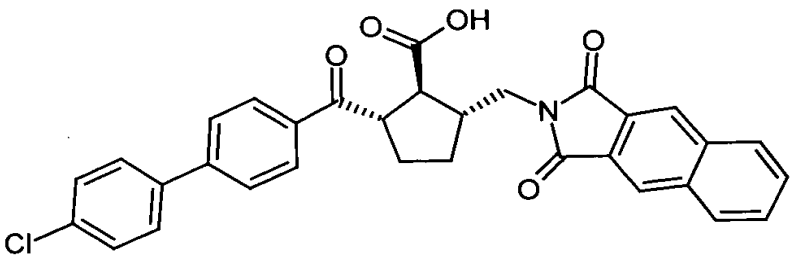
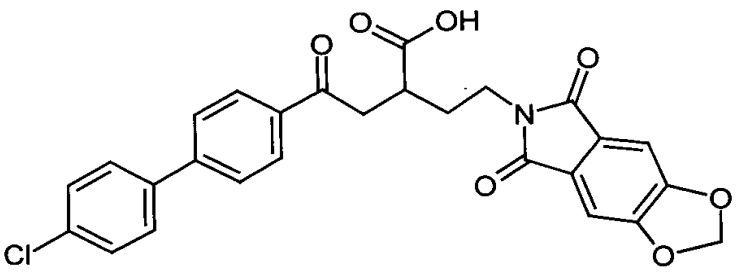
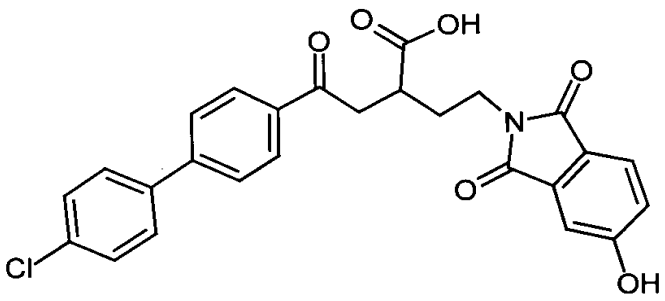
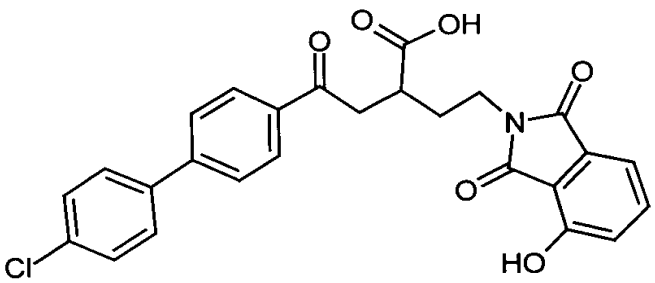
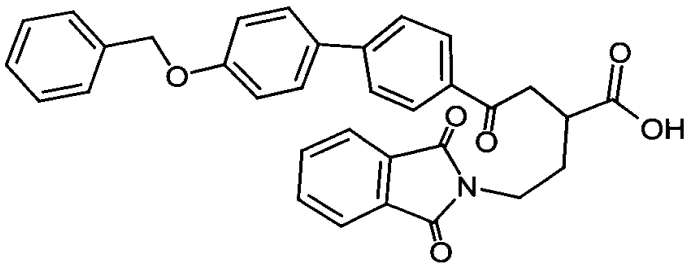


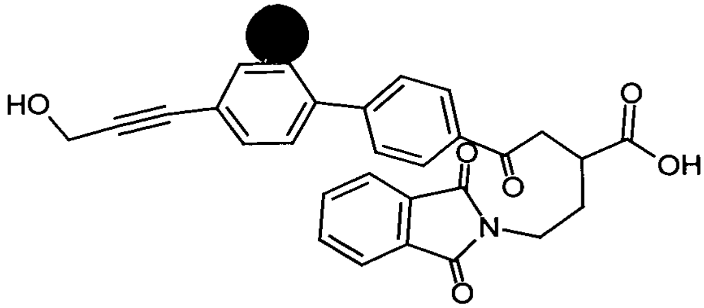


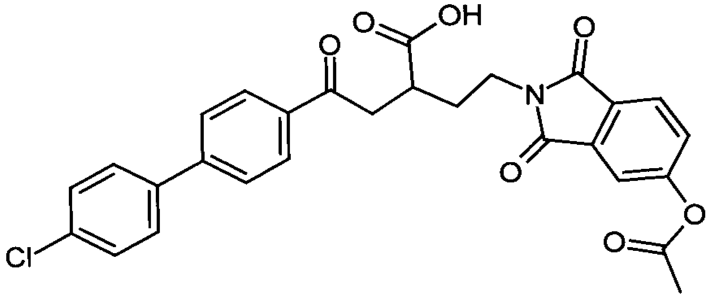


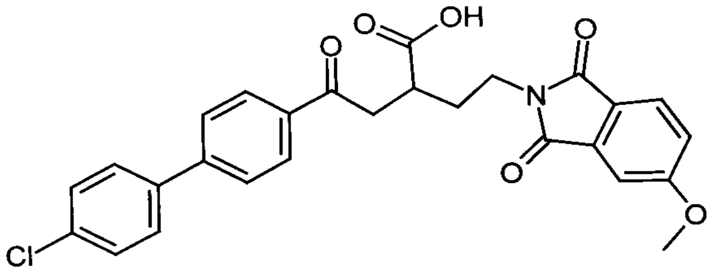


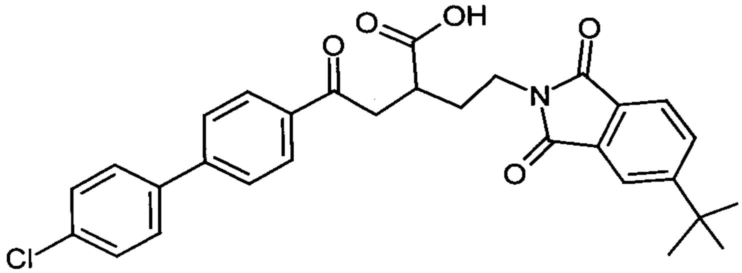


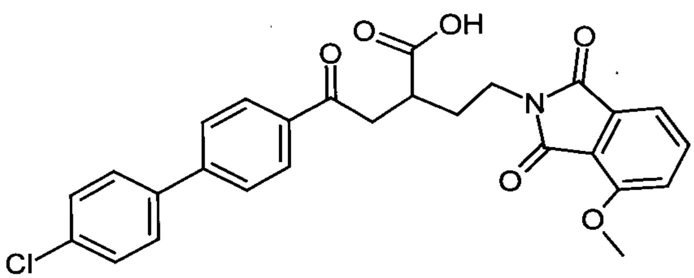






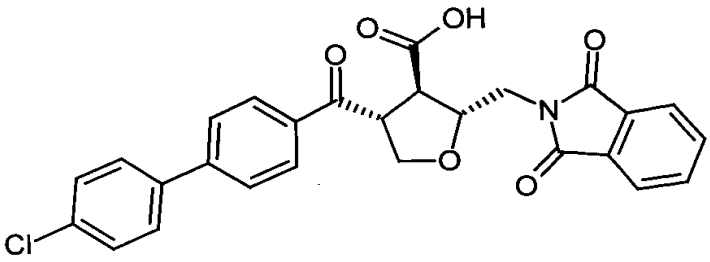


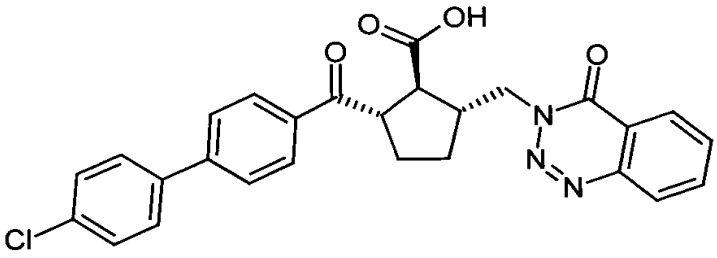


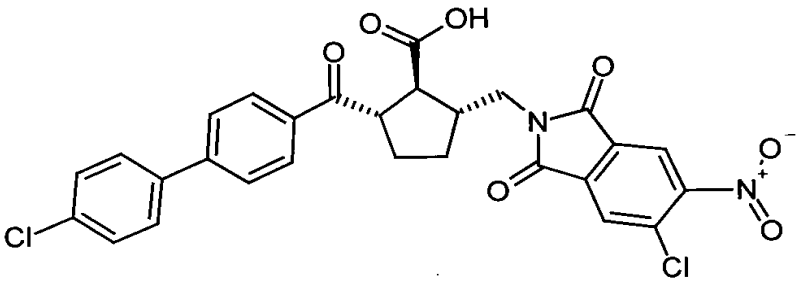


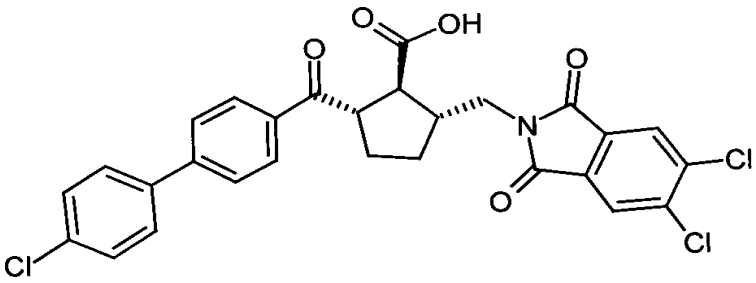


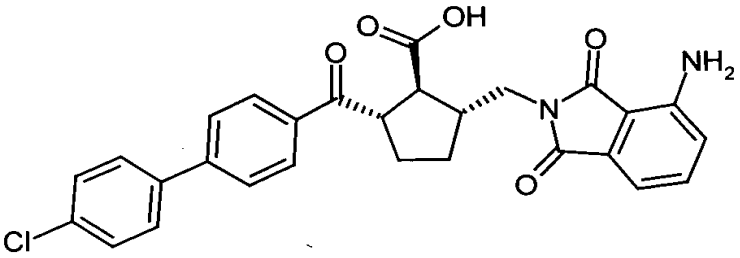


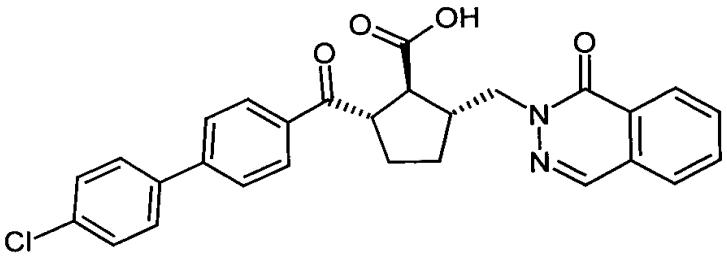


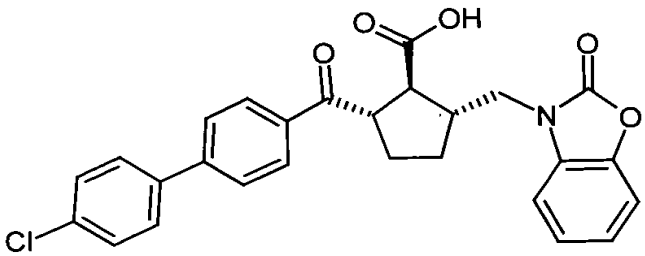
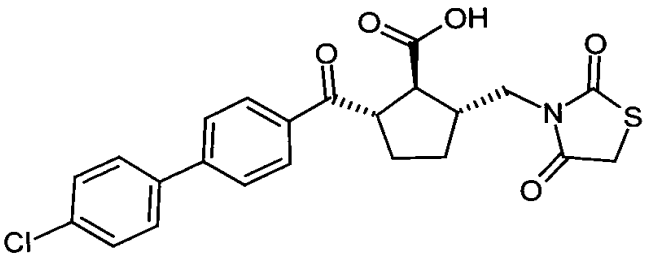
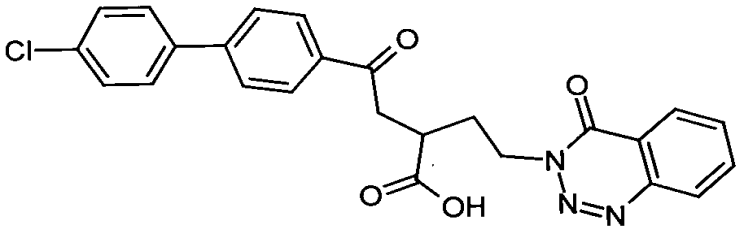
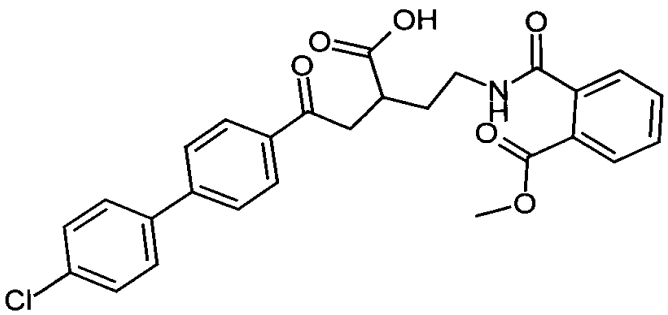
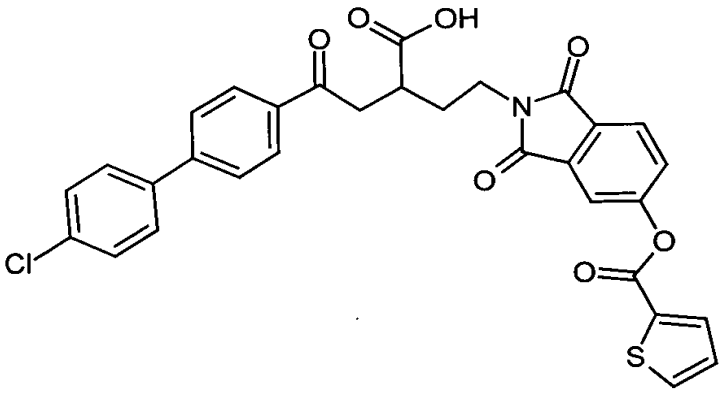


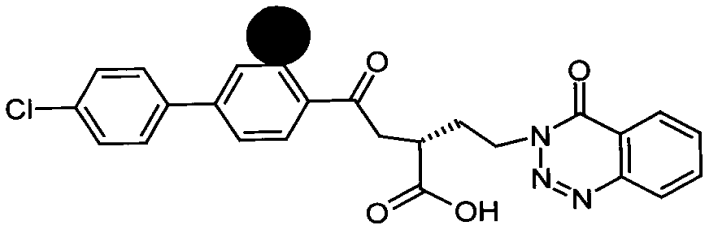






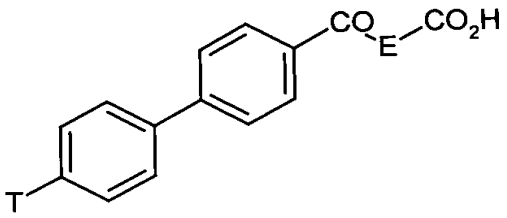




[for the manufacturing of drugs for the treatment and prevention of respiratory diseases].

9. (Amended) A method of treating or preventing a respiratory disease, comprising administering to a mammal an effective amount of a compound [Use of compounds] of the general formula (I')



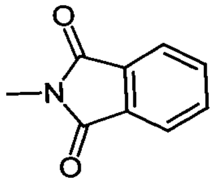
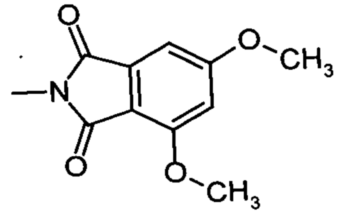
(I')

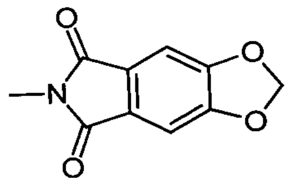
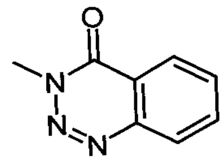
wherein

T is (C_1-C_4)-alkoxy, chloride, bromide, fluoride, acetoxy, hydroxy, cyano, trifluoromethyl or trifluoromethoxy,

CO-E-CO_2H represents a 3-carboxyl-5-R^7-pentan-1-on-1-yl- or a 2-carboxyl-3-(R^7-methyl)-cyclopentan-1-yl)carbonyl-residue, and

R^7 represents a group of the formula

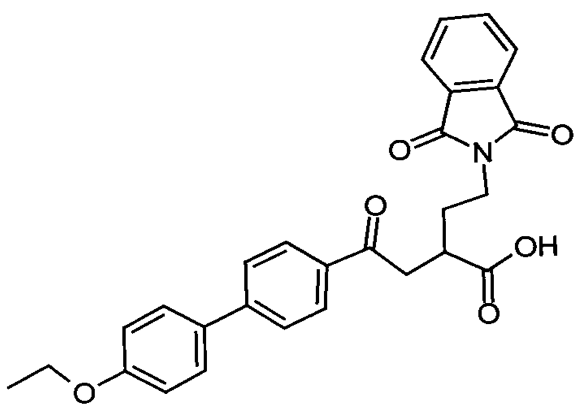
 ,  ,

 , or 

and their salts[, for the manufacturing of drugs for the treatment and prevention of respiratory diseases].

10. (Amended) A method of treating or preventing a respiratory disease, comprising administering to a mammal an effective amount of the compound [Use of the compound]

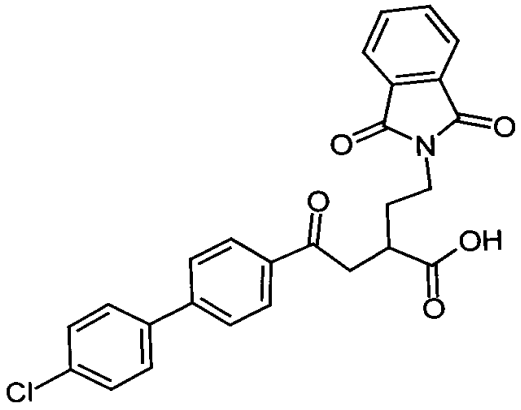
(+)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-(4'-ethoxy[1,1'-biphenyl]-4-yl)-4-oxobutanoic acid,



[for the manufacturing of drugs for the treatment and prevention of respiratory diseases].

11. (Amended) A method of treating or preventing a respiratory disease, comprising administering to a mammal an effective amount of the compound

[Use of the compound] (+)-4-(4'-chloro[1,1'-biphenyl]-4-yl)-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-oxobutanoic acid



[for the manufacturing of drugs for the treatment and prevention of respiratory diseases].

12. canceled.

14. The method of claim 1, 9, 10 or 11, wherein said respiratory disease is selected from the group consisting of [Use of a compound according to any one of claims 1 to 6 or 9 to 11 for the treatment and prevention of] asthma; chronic obstructive pulmonary diseases including chronic bronchitis and emphysema; cystic fibrosis; bronchiectasis; adult respiratory distress syndrome (ARDS); allergic respiratory disease including allergic rhinitis; diseases linked to TNF_{α} production including acute pulmonary fibrotic diseases, pulmonary sarcoidosis, silicosis, coal worker's pneumoconiosis, alveolar injury in mammals, such as human, a farm animal or a domestic pet.

15. canceled.

16. (Amended) A pharmaceutical [C]composition [containing] comprising a compound[s] according to Claim 7 or 8 and a pharmaceutically acceptable carrier.

17. (Amended) A method of treating or preventing [Composition according to Claim 16 for the treatment and prevention of] acute and chronic inflammatory processes, comprising administering to a mammal an effective amount of a compound according to claim 7 or 8.